UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,218	08/18/2000	Olga Yurieva	600-1-179N CON	6461

7590 03/03/2004

MICHAEL L GOLDMAN
NIXON PEABODY LLP
CLINTON SQUARE
P O BOX 31051
ROCHESTER, NY 14603-1051

EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,218	YURIEVA ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *1-6,13-21,24-26,31-33,35-43,48-51,55-60 and 64-67,73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12,22,23,27-30,34,44,45,52,61 and 68-72* is/are rejected.

7)☒ Claim(s) *46,47,53,54,62 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment of the previous sequence listing of 11/24/2003 is acknowledged. Claims 1-73 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group II, Claims 7-15, 22-42, 44-64 and 68-72 and Group B (i.e. the dnaX nucleic acid of SEQ ID NO: 3) in the paper of 7/28/2003 is acknowledged. The traversal is on a number of ground(s). Firstly applicants submit that the inventions of Groups I, II and III are sufficiently related inventions, i.e., both relate to polymerase subunits that are capable of use together to form a clamp loader of a polymerase III enzyme. Applicants characterization of the relationship between the inventions of Groups I and II is found persuasive, and as applicants assert the inventions of Groups I and II are related.

Inventions I, II, and III are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, inventions I and II each have a separate utility such as their use as hybridization probes for the detection of different nucleic acid molecules and, inventions III and IV each have a separate utility such as their use in the synthesis of antibodies to be used for the detection of different polypeptide molecules. See MPEP § 806.05(d).

Applicants submit that restriction among Groups A-E is improper based merely upon the earlier asserted position that inventions A-E are "chemically and structurally

unrelated". Applicants submit that the PTO ignores that the inventions of Groups A-E are related inventions, capable of use together.

As discussed above, with respect to Groups I-III, the species A- E are related as subcombinations capable of use together.

Inventions A-E are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, inventions A-H each have a separate utility such as their use as hybridization probes for the detection of different nucleic acid molecules. See MPEP § 806.05(d). Therefore, as discussed above (for Groups I-IV) inventions A-H are also subject to restriction.

Applicants finally request from a practical perspective that the PTO consider examining the nucleic acids of dnaX (encoding tau and gamma subunits) and dnaE (encoding alpha subunit), as this subject matter would be potentially interfering subject matter relative to the subject matter of U.S. Patent No. 6,238,905 to McHenry et al.

Applicants further arguments are not found persuasive because based on the reasons previously stated and stated above it is believed that the previous restriction requirement is proper and necessary to ensure that the burden of search and examination of the elected invention is not so great, so as to preclude a high quality search and examination. It is believed that the additional search and examination requested by applicants would not allow for the highest quality product comprising a proper search and examination.

Applicant is reminded that claims 11, 44, 61 and 68-72 link(s) inventions (A) through (E). The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 11, 44, 61 and 68-72.

Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claims 1-6, 13-21, 24-26, 31-33, 35-43, 48-51, 55-60 and 64-67 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the

list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures filed on 8/18/2000 and 8/11/2003, are acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

The sequence listing for SEQ ID NO: 1 lists a 2007 bp nucleic acid sequence while figure 4A and the description of figure 4A lists a sequence as SEQ ID NO: 1 that is 2027 bp. Appropriate correction and/or explanation is requested.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: Applicants attention is drawn to the figures which contain nucleotide and/or amino acid sequences and MPEP **2422.02** - The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures

> ...It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequen identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

Specifically figures 2, 5, 6, 15 and 16-19 contain nucleic and/or amino acid sequences which should be described with a SEQ ID NO. as discussed above.

On page 36, line 13, applicants recite "...dua X, dua E and dua N and combinations therof..." This should be "...*dna*X, *dna*E and *dna*N and combinations thereof...".

On page 36, line 15, applicants recite "...dua X" This should be "...*dna*X".

On page 36, line 18, applicants recite "...nucleo ??????". This should be "nucleotide".

Appropriate correction is required.

Claim Objections

Claims 8, 11, 12, 22, 23, 27, 28, 29, 30, 34, 44, 46, 47, 53, 54, 62 and 63 are objected to because of the following informalities:

Claims 8 recites "alleles thereof. And active fragments thereof." It appears that the first period should be a comma instead of a period.

Claims 46 and 47 are dependent on rejected claim 45.

Claims 53 and 54 are dependent on rejected claim 52.

Claims 11, 12, 22, 23, 27, 28, 29, 30, 34, 44, 62 and 63 are directed to nonelected subject matter. (i.e. SEQ ID NOs: 4, 5, 87, 95 and 107).

Claims 62 and 63 are dependent on rejected claim 61.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite in that it is confusing in the recitiation positions 1 to 2027 of SEQ ID NO: 1" because as stated above the sequence listing for SEQ ID NO: 1 only lists a 2007 bp sequence.

Claim 8–10 are indefinite in that the phrase "active fragments thereof" is unclear and confusing. A biologically active protein may encompass a variety of different biological activities. These include but are not limited to immunological activity, such as acting as an antigen for an antibody; regulatory activity, such as that exhibited by many proteins which control transcription and/or translation of not only their encoding nucleic acids but other nucleic acids as well; or enzymatic activity, for example, polymerase activity. It is not clear what is encompassed by the "activity" of the polypeptides encoded by the claimed polynucleotides and if it includes biological activities in addition to enzymatic activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45 and 52, 61 and 68-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7-10 are directed to all possible isolated polynucleotides encoding a τ subunit of a *Thermus thermophilus* DNA polymerase III-type enzyme, wherein said τ subunit has a molecular weight of about 58,000 daltons (claim 7), wherein said amino acid residue sequence is represented by the formula shown in SEQ ID NO: 2 or the polynucleotide sequence of positions 132 to 1713 or 1 to 2027 of SEQ ID NO: 1, conserved variants thereof, analogs thereof, muteins thereof, alleles thereof, active fragments thereof and combinations thereof.

Claims 11, 12, 22, 23, 28, 29, 30, 34 and 52, 61 and 68-72, are directed to all isolated nucleic acid molecules encoding a single subunit of a DNA polymerase III-type enzyme found in a thermophilic bacterium, selected from the group consisting of dnaX, variants, including conserved variants analogs and fragments and combinations thereof, capable of functioning in DNA amplification and sequencing, vectors, host cells, expression systems and methods comprising said nucleic acid (claims 11, 12, 22, 23, 28, 29, 30, 34, 52, 61, 68-72).

Claims 44 and 45 are directed to all isolated DNA molecules encoding a protein subunit of DNA polymerase III-type enzyme from a thermophilic bacterium wherein the subunit is τ and has a molecular weight of 58 kD.

There is no disclosure of any particular structure to function/activity relationship in the disclosed species encompassed by the rejected claims. The specification also

fails to describe additional representative species of these polynucleotides and the encoded polypeptides by any identifying structural characteristics or properties other than the activities and molecular weight, recited in the claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45 and 52, 61 and 68-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding a τ subunit of a DNA polymerase III-type enzyme, wherein said τ subunit has an amino acid residue sequence represented by the formula shown in SEQ ID NO: 2, does not reasonably provide enablement for any polynucleotide encoding a τ subunit of a DNA polymerase III-type enzyme, wherein said τ subunit has a molecular weight of 58,000 daltons. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 7-10 are so broad as to encompass any polynucleotide encoding a τ subunit of a *Thermus thermophilus* DNA polymerase III-type enzyme, wherein said τ subunit has a molecular weight of about 58,000 daltons, wherein said amino acid residue sequence is represented by the formula shown in SEQ ID NO: 2 or the polynucleotide sequence of positions 132 to 1713 or 1 to 2027 of SEQ ID NO: 1, conserved variants thereof, analogs thereof, muteins thereof, alleles thereof, active fragments thereof and combinations thereof.

Claims 11, 12, 22, 23, 28, 29, 30, 34 and 52, 61 and 68-72, are so broad as to encompass any nucleic acid molecules encoding a single subunit of a DNA polymnerase III-type enzyme found in a thermophilic bacterium, selected from the group consisting of dnaX, variants, including conserved variants analogs and fragments and combinations thereof, capable of functioning in DNA amplification and sequencing, vectors, host cells, expression systems and methods comprising said nucleic acid.

Claims 44 and 45 are so broad as to encompass any DNA molecule encoding a protein subunit of DNA polymerase III-type enzyme from a thermophilic bacterium wherein the subunit is τ and has a molecular weight of 58 kD.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and DNA molecules broadly encompassed by the claims, including those yet to be discovered or identified. The claims rejected under this section of U.S.C. 112, first paragraph, place minor structural limits on the claimed polynucleotides and DNA molecules Since the amino acid sequence of a protein (and hence its encoding DNA) determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that DNA molecule which comprises the amino acid sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Further applicants have given no guidance where one could obtain other species encompassed by the claimed genus.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any isolated polynucleotide from a thermophillic bacterium which encodes a τ subunit of a DNA polymerase III-type enzyme because the specification does not establish: (A) regions of the protein structure which may be modified without effecting τ subunit activity; (B) the general tolerance of τ subunits to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a DNA polymerase III enzyme τ subunit with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the delta subunit activity and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those DNA molecules of the claimed genus which encode a polypeptide with DNA polymerase III enzyme τ subunit activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any DNA molecule from a thermophilic bacterium, encoding a DNA polymerase III-type enzyme τ subunit. The scope of the

claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

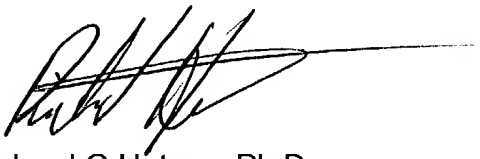
Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 27 appears to employ a novel strain of vector pET*dnaX*. Since the vector pET*dnaX* is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The vector pET*dnaX* is not fully disclosed, nor has it been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the vector pET*dnaX*. Accordingly, it is deemed that a deposit of the vector pET*dnaX* should have been made in accordance with 37 CFR 1.801-1.809.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
3/1/2004